the formation of a sulfone. Taking into account the absence of an ethylenic linkage, as well as the nature of the functional groups and the ratio of hydrogen to carbon, it is evident that biotin must contain a bicyclic ring system. In two papers recently come to hand, Kögl and co-workers[4,5] arrived at similar conclusions and they present evidence that the sulfur is part of a ring.

We should now like to report the isolation of adipic acid ($C_6H_{10}O_4$) from the degradation products obtained by treatment of the diaminocarboxylic acid with nitric acid or alkaline permanganate. The adipic acid was purified by crystallization from ether and sublimation *in vacuo*. The melting point of the purest samples was 152–153°.[6] A mixture of the isolated material with an authentic sample of adipic acid showed no depression in melting point. The neutral equivalent determined by Dr. Julian Rachele of this Laboratory was found to be 73 in agreement with the theory. To characterize the acid further we have prepared the diamide, m. p. 223–226°, as well as the di-β-naphthylamide, m. p. 266–267°, and both of these compounds proved to be identical with the analogous derivatives prepared from the authentic sample of adipic acid.

It is quite obvious that the finding of a 6-carbon straight chain moiety in the biotin molecule greatly reduces the number of possible structures that might be ascribed to biotin. We prefer to reserve, however, a discussion of structure until experiments underway conclusively demonstrate whether one of the carboxyl groups of the adipic acid is the original carboxyl group of biotin.

(4) F. Kögl and L. Pons, *Z. physiol. Chem.*, **269**, 61 (1941).

(5) F. Kögl and Th. J. de Man, *ibid.*, **269**, 81 (1941).

(6) All the melting points given are micro melting points.

DEPARTMENT OF BIOCHEMISTRY
CORNELL UNIVERSITY MEDICAL COLLEGE
NEW YORK, N. Y.
KLAUS HOFMANN
DONALD B. MELVILLE
VINCENT DU VIGNEAUD

RECEIVED OCTOBER 23, 1941

THE TETRAACETYL-β-GLUCOSIDE OF DESOXYCORTICOSTERONE

Sir:

A number of considerations are consistent with the suggestion that the true hormone of the adrenal cortex may be a substance resembling a glycoside retaining the corticosterone type of structure as the aglycone. Some light may be thrown on this speculation by a study of the physiological action of synthetic compounds containing the corticosteroid nucleus linked to a sugar residue. The formation of the glucoside linkage in desoxycorticosterone therefore has been investigated. This work was in progress at the time of the announcement by Zwemer, Lowenstein and Pines [*Endocrinology*, **27**, 945 (1940)] of their intention to pursue similar lines of research.

Since the work described below was completed, British Patent 525,307 has come to my attention [*Chem. Abst.*, **35**, 6599 (1941)]. The claims involve the preparation of the tetraacetylglucoside of desoxycorticosterone by the conventional Helferich silver oxide method. The melting point, 175–176°, is in agreement, but no other physical constants, analysis or yields are recorded.

Because of the general inaccessibility of desoxycorticosterone it seemed necessary to investigate a technique for the small-scale preparation of glucosides of steroids. Cholestanol was chosen for this work since both the α- and β-glucoside tetraacetates are easily isolated and have been well characterized [Linstead, THIS JOURNAL, **62**, 1766 (1940)]. In the present work the Zemplén and the Helferich methods were adapted to the semi-micro preparation of the α- and β-isomers, respectively. From 30-mg. samples of sterol the tetraacetyl-α-glucoside was obtained in 35–40% yields; in the case of the β-isomer the yields were higher, 52–54%. A report of this work will appear in detail at a later date.

The Helferich silver oxide method on 25.7-mg. samples of desoxycorticosterone gave the tetraacetyl-β-glucoside in yields of 10–14%. These low yields may be attributed to difficulty in isolation of the reaction product, doubtless explained by its soluble properties in comparison with the cholestanol derivatives. The success of the preparation seemed to depend principally upon the maintenance of anhydrous conditions. A mixture of desoxycorticosterone (25.7 mg.), acetobromoglucose (63.6 mg.), silver oxide (40 mg.) and drierite (about 20–30 mg.) in chloroform or benzene (0.2 cc.) was sealed in a small soft glass tube and allowed to shake for twenty-four hours. The filtrate and washings were evaporated to dryness in a stream of air, and the residue treated with ether (1.7 cc.). On standing several days colorless crystals of the tetraacetyl-β-glucoside separated, yield 5–7 mg., m. p. 170–173° (cor.). Crystallization from 50% alcohol gave glistening clusters of colorless needles, m. p. 176–176.5° cor.

Anal. (Microanalysis by Arlington Laboratories). Calcd. for $C_{35}H_{48}O_{12}$: C, 63.62; H, 7.32.

Found: C, 63.39; H, 7.31. *Rotation.* 10.3 mg. dissolved in 2.0 cc. of chloroform gave a rotation of +0.82° at 23.6°; l, 2 dm.; $[\alpha]^{23.6}\mathrm{D}$ +80°; C = 0.515.

Biological tests on the tetraacetate and deacetylated material are being conducted by Dr. E. S. Gordon of the University of Wisconsin Medical School.

I am indebted to Schering Corporation for supplies of desoxycorticosterone acetate.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF WISCONSIN
MADISON, WISCONSIN WILLIAM S. JOHNSON

RECEIVED OCTOBER 14, 1941

THE EFFECT OF METALLIC HALIDES ON THE REACTION OF ORGANOLITHIUM COMPOUNDS WITH ALKYL AND ARYL HALIDES

Sir:

It has recently been found in this Laboratory[1] that small amounts (2–5 mole per cent.) of metallic halides profoundly affect the reactions of organomagnesium halides with a variety of organic compounds. Specifically, an ether solution of *p*-tolylmagnesium bromide, which does not react with phenyl bromide under the usual conditions, reacts readily with that compound in the presence of cobaltous chloride to give high yields of *p,p'*-bitolyl, along with biphenyl (trace), terphenyl and other polyphenyls. Ethylmagnesium bromide reacts rapidly with phenyl bromide in the presence of cobaltous halides to give ethane, ethylene, biphenyl (trace) and polyphenyls.

This type of catalytic effect has now been observed in reactions of organolithium compounds with alkyl and aryl halides. Whereas, under normal conditions, phenyllithium reacts to a negligible extent with phenyl bromide, reaction proceeds rapidly in the presence of 5 mole per cent. of cobaltous bromide, to give high yields of biphenyl along with smaller quantities of terphenyl and polyphenyls. With ethyl bromide, phenyllithium reacts normally in ether solution to give ethylbenzene. In the presence of 2–5 mole per cent. of cobaltous bromide the products are biphenyl, ethane and ethylene. Butyllithium reacts normally in ether solution with phenyl bromide to give butylbenzene. No biphenyl or other solid or tarry material is formed. In the presence of 3–5 mole per cent. of cobaltous bromide, however, practically no butylbenzene is formed; the reaction products are biphenyl, terphenyl, and gases that appear to be a mixture of butane and butylene.

Experimental

In a typical experiment, to 100 ml. of a 1.06 N ether solution of phenyllithium at 0° was added 1.1 g. of cobaltous bromide (0.005 mole). A black coloration immediately appeared. To this mixture was added 0.1 mole of bromobenzene. A vigorous reaction ensued. The mixture was stirred for three hours, allowed to stand an additional twelve hours, and then poured onto cracked ice and acidified with dilute nitric acid. The layers were separated and the water layer extracted twice with ether. The combined ether layers were then treated with small quantities of bicarbonate solution, which were added to the water layer. Titration of an aliquot of this solution for bromide ion and analysis of the original phenyllithium solution indicated that 54% of the bromobenzene entered into the reaction, due allowance being made for the halide from cobaltous bromide. The ether layer yielded 8.5 g. of biphenyl and 1.0 g. of a mixture of terphenyl and polyphenyls. If corrected for the biphenyl present in the phenyllithium solution (0.9 g.) 7.6 g. of this product was formed in the reaction. In a control experiment and excluding the cobaltous bromide less than 2% of the bromobenzene had reacted and only the amount of biphenyl indicated above was found.

The promotion of the reactions that do not otherwise occur is striking, but it is perhaps even more significant that the nature of the products and, therefore, of the reaction mechanism, is fundamentally altered in the other cases cited.

These reactions will be recorded in greater detail later. It is the intention to study the effect of metallic halides in the condensation of organolithium (as well as other organometallic) compounds with a variety of organic substances (unsaturated compounds, acid halides, aldehydes, ketones).

GEORGE HERBERT JONES CHEMICAL LABORATORY
UNIVERSITY OF CHICAGO M. S. KHARASCH
CHICAGO, ILLINOIS W. B. REYNOLDS

RECEIVED AUGUST 19, 1941

---

[1] For reference see Kharasch and Fields, THIS JOURNAL, **63**, 2316 (1941).